

REMARKS

Claims 1-37, 40-44, and 46-60 are pending in the application. Claims 28-37 and 40-44 were withdrawn from consideration, pursuant to a Restriction Requirement. Claim 60 was objected to, and claims 1-27 and 46-60 were rejected. The objection and rejections are addressed below.

Before addressing the objection and rejections, Applicants note that claim 1 has been amended to require a single reading, in a single assay of the presence or proportionally cumulative amount of proANP and proBNP, or fragments thereof. Support for this amendment can be found, for example, in paragraphs 123, 146, 149, and 167 of the application as published. Central to the invention is that a single assay provides a single reading indicating the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing the individual presence or amount of proANP and proBNP in the sample. The invention is based on the discovery that detection of the presence or proportionally cumulative amount of proANP and proBNP in a single reading is sufficient to determine activation or inactivation of the ANP and BNP hormonal systems. Such an approach provides substantial benefits with respect to ease of use and efficiency and, as discussed further below, is not taught or suggested in the prior art.

Applicants further note the addition of new claim 61, which specifies that detecting of the presence or proportionally cumulative amount of atrial and brain natriuretic peptide prohormones (proANP and proBNP) or fragments thereof in a sample according to the method of claim 1 is done relative to a reference level for determining activation or inactivation of the ANP and BNP hormonal systems. Support for this amendment can be found, for example, in paragraph 0288 of the published application. No new matter has been added.

Objection

Claim 60 was objected to for being in improper dependent form. Claim 60 has been amended to properly depend from claim 47 and, therefore, the objection can be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 18, 19, 22-24, 49, 50, 56, and 57 were rejected under 35 U.S.C. § 101 on the basis that these claims are directed to non-statutory subject matter. The Examiner states that the claims as written do not sufficiently distinguish the claimed subject matter from a polypeptide that naturally exists in an organism, because the claims do not point out any non-naturally occurring differences between the claimed sequences and naturally occurring products. Claims 18, 19, 23, 49, and 56 have been amended to specify a “fusion polypeptide agent,” claim 22 has been cancelled, and claims 24, 50, and 57 depend from claims 23, 24, and 50, respectively. Therefore, the claimed subject matter unambiguously does not include polypeptides that naturally exist in an organism, and the rejection under 35 U.S.C. § 101 can be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-17, 19, 20, 23, 24, 46-50, 52-57, 59, and 60 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on several grounds, which are addressed as follows.

Claim 1 was rejected for omitting an essential step. In particular, the Examiner states that claim 1 does not recite a step indicating how those skilled in the art can conclude whether there is an increase or decrease in the peptides of interest. In response, Applicants submit that a separate step for this purpose is not essential. Rather, the detecting step recited in the claimed method is sufficient to provide the indication of an increase or decrease to a user of the method.

In particular, as is known in the art, assay systems can be pre-calibrated so that detection by the system of the mere presence (or absence) of a target, or detection by the system of an amount of a target, is indicative of the desired determination (see, e.g., paragraphs 134 and 315 of the publication of the present application). In view of this, Applicants submit that claim 1 does not require any additional steps and, therefore, this rejection can be withdrawn.

The Examiner also rejected claims 3 and 47 for omitting an essential step. Specifically, the Examiner states “one of ordinary skill in the art would be unable to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of contacting the sample with an agent comprising atrial and brain natriuretic peptide prohormones as recited in claim 3 [or claim 47].” Claims 3 and 47 depend from claim 1 and merely specify the nature of certain reagents to be used in the method of claim 1. Thus, the comments set forth above with respect to claim 1 apply in this rejection as well. Further, an example of an embodiment of the method of claims 3 and 47 is recited in the specification as including the use of a fusion polypeptide agent as a calibration reagent (see, e.g., paragraphs 134 and 315 of the published application). Therefore, because all of the steps necessary to perform the claimed method are present in claim 1, the rejection of dependent claims 3 and 47 for indefiniteness should be withdrawn.

The Examiner rejected claims 10 and 19, because it is unclear to the Examiner whether Applicants require there to be two sequences and because the Examiner considers the phrase “comprises or consists of” to be unclear. Claims 3 (from which claim 10 depends) and 19 each have been amended to recite a “fusion polypeptide agent.” Therefore, the amended claims unambiguously reference a single linked molecule containing two sequences. Furthermore, claims 10 and 19 have been amended to recite “comprises.” In view of these amendments, the

rejection of claims 10 and 19 can be withdrawn.

Claim 20 was rejected as being indefinite, because it is unclear to the Examiner how the sequence identifiers in claim 20 relate to the polypeptides recited in claim 19. Claim 20 has been amended to include the term “respectively,” which unambiguously indicates that each of the recited sequences falls within the corresponding subclause of claim 19 (e.g., the first recited sequence of claim 20, SEQ ID NO:13, corresponds to the first subclause of claim 19, (a)). In view of this amendment, this rejection can be withdrawn.

Claim 23 was rejected as not clearly specifying to what a “polypeptide” refers. Claim 23 has been amended to specify that the polynucleotide encodes a “fusion polypeptide agent.” As the amended claim clearly recites a single molecule that encodes both polypeptide sequences, this rejection can be withdrawn.

Claims 47 and 59 were rejected as being vague and indefinite for reciting the ability to bind one polypeptide “and/or” another. Claim 47 has been amended to specify that the first binding substance binds to the materials specified in parts (c), (d), and (e) of the claim, and claim 59 has been amended to specify that the first binding substance binds to the materials specified in parts (a), (b), and (c) of the claim. Applicants thus request that this rejection be withdrawn.

Claim 49 was rejected as being vague and indefinite for not clearly indicating whether a single molecule comprises both polypeptides. Claim 49 has been amended to recite a “fusion polypeptide agent,” which unambiguously indicates that a single molecule includes both polypeptide sequences. In view of this amendment, this rejection can be withdrawn.

Claim 52 was rejected as not clearly indicating whether the binding substance must bind to two or four polypeptides. The claim has been amended to clearly indicate that the claim requires that the binding substance bind to at least two of the recited polypeptides. In view of

this amendment, this rejection can be withdrawn.

Claim 60 was rejected as being vague and indefinite for reciting a method of claim 49, which recites an agent. Claim 60 has been amended to recite a method of claim 47, which also recites a method. In view of this amendment, this rejection can also be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-6, 9-17, 46-48, 52-55, and 59 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement over the full scope of the claims. Specifically, the Examiner states that the specification, while being enabling for the full length or extracellular binding domain of natriuretic receptor GC-A, is not enabling for the use of variant natriuretic receptors. In the interest of expediting prosecution, Applicants have amended claims 5 and 48 to no longer recite subject matter considered by the Examiner as not being enabled: sequences with at least 70% identity to SEQ ID NO:33 and species homologues or allelic variants of GC-A. Because the claims no longer recite variants of GC-A, the rejection for lack of enablement over the full scope of the claims can be withdrawn.

Claims 1-6, 9-17, 24, 46-48, 50, 52-55, and 59 were rejected under 35 U.S.C. § 112, first paragraph for lack of adequate written description. The Examiner states that sequences with greater than 70% identity to SEQ ID NO:33 are not described in the specification in such a way as to reasonably convey to those skilled in the art that the inventors had possession of the invention at the time the application was filed. Claims 5 and 48 have been amended to eliminate recitation of sequences with at least 70% identity to SEQ ID NO:33. In view of these amendments, the rejection of claims 1-6, 9-17, 46-48, 52-55, and 59 should be withdrawn.

The Examiner rejected claims 24 and 50, because they encompass a genus of nucleic acid

molecules that hybridize under medium or high stringent conditions to SEQ ID NOs:7-12, species homologues or allelic variants thereof, or sequences complementary to the recited sequences. However, the genus of claimed nucleic acid molecules is much smaller than the Examiner acknowledges, because claims 24 and 50 depend from claim 23, which requires that the polynucleotide “encodes a fusion polypeptide agent according to claim 18.” There is a well-understood relationship between the sequence of a polynucleotide and the sequence of the polypeptide it encodes. Based on the limitation that the nucleic acid molecules encode a fusion polypeptide agent according to claim 18, it would be readily apparent to those skilled in the art that the Applicants were in possession of the invention at the time the application was filed. Therefore, the rejection of claims 24 and 50 for inadequate written descriptions should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 16, and 17 were rejected under 35 U.S.C. § 103(a) for obviousness over Clerico et al., J. Endoc. Invest. 21:170-179, 1998, in view of Clerico et al., Clin. Chemistry 46:1529-1534, 2000. Applicants request that this rejection be reconsidered and withdrawn.

Before addressing the cited references, Applicants note that, as discussed above, claim 1 has been amended to require a single reading, in a single assay of the presence or proportionally cumulative amount of proANP and proBNP, or fragments thereof. Central to the invention is that a single assay provides a single reading indicating the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing the individual presence or amount of proANP and proBNP in the sample. The invention is based on the discovery that detection of the presence or proportionally cumulative amount of proANP and proBNP in a single reading is

sufficient to determine activation or inactivation of the ANP and BNP hormonal systems. Such an approach, which provides substantial benefits with respect to ease of use and efficiency, is not taught or suggested in the cited references.

Clerico (1998) was cited for teaching the measurement of plasma ANP and BNP individually in patients with heart failure. Clerico (2000) was cited for teaching that cardiac natriuretic hormones are a family of related peptides, including ANP, BNP, and N-terminal portions of proANP and proBNP, which may be present in greater amounts in plasma than ANP and BNP. The Examiner concludes that it would have been obvious to use the methods of Clerico (1998) to detect the different natriuretic protein forms taught by Clerico (2000), particularly in view of the teaching of Clerico (2000) of the higher concentrations of these forms in plasma. The Examiner further concludes that “one of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays. . . would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce to the costs of said assays.”

However, nowhere does either Clerico (1998) or Clerico (2000) teach or suggest the measurement of the presence or proportionally cumulative amount of proANP and proBNP in a single reading, in a single assay. The M.P.E.P § 2141.02 VI states “a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)” (emphasis original).

When considered as a whole, Clerico (1998) provides a rationale for measuring ANP and BNP *separately* as “the data reported in Figure 3 suggest that the BNP assay is more useful than the ANP assay for discriminating between normal subjects and patients with cardiomyopathy,

even including those with only mild symptoms” (page 176, column 1). Furthermore, Clerico (2000) states

[A]lthough ANP and BNP bind to the same specific receptors, they have different types of metabolism and spectra of biological activity, and their production and secretion may be regulated differently in humans. It has been suggested that there may be different pools of intracellular natriuretic peptides that can respond separately to the same hemodynamic events (e.g., overload for ANP) or to the same pathology-related factors (e.g., cardiac hypertrophy for BNP). (Page 1530, column 1).

Based on these statements, Clerico (1998) and Clerico (2000) teach the desirability of distinguishing between ANP and BNP levels and, therefore, teach away from the claimed methods, which require a single reading, in a single assay, showing the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides.

The rejection of claims 1, 16, and 17 for obviousness based on Clerico (1998) and Clerico (2000) should be withdrawn, because it would not have been obvious to those skilled in the art to measure proANP and proBNP using a method that does not distinguish between the two polypeptides, such as that now claimed.

Claims 2-4, 7-15, 46, 47, 52-54, and 59 were rejected for obviousness over Clerico (1998), in view of Clerico (2000), and further in view of Buechler et al., U.S. Patent No. 7,341,838.

The Clerico references were cited for the reasons discussed above. Buechler ('838) was cited for describing amino acid sequences bearing similarity to SEQ ID NOs:3 and 6, which are stated by Buechler ('838) to correspond to proANP and proBNP. The Examiner states that those of skill in the art would have recognized that antibodies that recognize the sequences of Buechler ('838) would also recognize the sequences of the present claims, and that Buechler ('838)

teaches measuring the amounts of ANP and BNP-related fragments by using antibodies, including bivalent antibodies. In view of these teachings, the Examiner concludes that it would have been obvious to modify the methods of Clerico (1998 and 2000) by substituting the sequences taught by Buechler ('838) and utilizing bispecific antibodies, as taught by Buechler ('838). Applicants respectfully disagree and request that this rejection be reconsidered and withdrawn.

As discussed above, a central feature of the present invention is the detection of the presence or proportionally cumulative amount of both proANP and proBNP-related sequences in a single reading, in a single assay. Also as discussed above, it would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler ('838) does not teach or suggest testing for the presence or proportionally cumulative amount of proANP and proBNP-related sequences in a single reading, in a single assay. In view of the above, Applicants request that this rejection be reconsidered and withdrawn.

Claims 5, 6, 48, and 55 were rejected for obviousness over Clerico (1998), in view of Clerico (2000) and Buechler (U.S. Patent No. 7,341,838), and further in view of Bentivegna et al., WO 01/79231. Applicants request that this rejection be reconsidered and withdrawn.

The Clerico (1998 and 2000) and Buechler ('838) references were cited for the reasons described above. Bentivegna ('231) was cited for teaching a sequence that corresponds to SEQ ID NO:34 of the present application, which is the natriuretic receptor GC-A. The Examiner states that it would have been obvious to modify the methods of Clerico (1998 and 2000) and

Buechler ('838), by utilizing the GC-A receptor, which binds to both ANP and BNP, in place of antibodies against these proteins. Applicants respectfully request that this rejection be reconsidered and withdrawn for the reasons provided above with respect to the prior rejections for obviousness. In particular, none of the cited references, alone or in combination, provide any teaching or suggestion of a central feature of the present invention, in which a single assay provides a single reading indicating the presence or proportionally cumulative amount of proANP and proBNP, without distinguishing the individual levels of proANP and proBNP in the sample. Rather, in carrying out methods according to the cited references, those skilled in the art would utilize an assay that *distinguishes* between proANP and proBNP-related sequences. In view of this, Applicants ask that this rejection be reconsidered and withdrawn.

Claims 18-22, 49, and 56 were rejected for obviousness over Nakata et al., EP 1118329, 2001, in view of Buechler, U.S. Patent No. 7,341,838. Applicants request that this rejection be reconsidered and withdrawn, for the following reasons.

As an initial matter, Applicants note that claims 18-21, 49, and 56 have been amended to specify a fusion polypeptide agent and claim 22 has been cancelled. Support for these amendments can be found, for example, in paragraph 219 of the published application. Claims 18, 49, and 56 specify a fusion polypeptide agent comprising both proANP and proBNP-related sequences. Dependent claims 19-21 specify that the fusion polypeptide agent of claim 18 includes particular sequences (claims 19 and 20), or is labeled with a detectable label (claim 21).

Nakata ('329) was cited for teaching compositions including ANP and BNP-related sequences, such as α -ANP, α -ANP [4-28], α -ANP [5-28], BNP-26, BNP-32, and BNP-45, as well as certain ANP and BNP-related dimer and high molecular weight structures, and Buechler ('838) was cited for teaching certain ANP and BNP prohormone-related sequences. The

Examiner states that it would have been obvious to substitute the sequences of Nakata ('329) with those of Buechler ('838), and that it would have been obvious to those of skill in the art to make a fusion protein, "so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies (as disclosed by the '838 patent) to detect both proteins."

Applicants respectfully disagree with this rejection, as there is no teaching or suggestion in the cited references to make fusion polypeptide agents or other molecules including both proANP and proBNP-related sequences, as are required by the present claims. Such a teaching or motivation certainly does not come from Nakata ('329), which does not mention fusion proteins or immunoassays at all. As to Buechler ('838), the focus of this patent is detection of natriuretic protein peptides and fragments, with a focus on BNP. Buechler ('838) nowhere mentions detection of both proANP and proBNP-related sequences in an assay, and provides no teaching or suggestion of using fusion proteins including proANP and proBNP-related sequences. Buechler ('838) does mention bivalent antibodies, but only in a general listing of different types of antibodies, and certainly with no indication that such antibodies should detect both proANP and proBNP-related sequences. Thus, there is no teaching or suggestion of detecting both proANP and proBNP-related sequences in the cited references, and there is also no teaching or suggestion to make the fusion proteins noted by the Examiner. Applicants therefore request reconsideration and withdrawal of this rejection.

Claims 23-27, 50, 51, 57, and 58 were rejected for obviousness over Lewicki et al., U.S. Patent No. 5,212,286, and Simari, WO 00/71576. Applicants request that this rejection be reconsidered and withdrawn.

The Examiner states that it would have been obvious to combine the teachings of Lewicki

('286) and Simari ('576) to produce the claimed compositions. Furthermore, the Examiner states "the claims do not unambiguously recite polynucleotides encoding fusion proteins comprising proANP and proBNP. . . One could interpret the claims as reciting polynucleotides encoding separate sequences," and that "one of ordinary skill would be motivated to produce compositions comprising said polynucleotides as said polynucleotides could be used to efficiently produce both proANP and proBNP." The claims have been amended to unambiguously recite fusion polypeptide agents. Neither Lewicki nor Simari teach or suggest the use of proANP and proBNP-related sequences produced in a fusion polypeptide agent. Therefore, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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